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SHORT COMMUNICATION

Enantioseparation of 4C-Substituted Pyrrolidin-2-One Derivatives on Polysaccharide and Macrocyclic Glycopeptide Chiral Stationary Phases

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Abstract
To extend our previous studies concerning the enantioseparation of 4C-substituted pyrrolidin-2-one derivatives on polysaccharide-based chiral stationary phases with ethanol/*n*-hexane mobile phases, two commercially available immobilized chiral stationary phases [amylose derivatized with (S)-α-methylbenzylcarbamate, and cellulose derivatized with 3,5-dichlorophenylcarbamate] were studied. Also, efforts to use macrocyclic glycopeptide (vancomycin, ristocetin A, teicoplanin, and teicoplanin aglycone) chiral stationary phases under normal-phase mode for enantioseparations of 4C-substituted pyrrolidin-2-one derivatives were made. It was established that both polysaccharide chiral stationary phases show high chiral recognition ability: 12 enantiomeric pairs on chiral selector cellulose *tris* (3,5-dichlorophenylcarbamate) and 11 enantiomeric pairs on chiral selector amylose *tris* [(*S*)-α-methylbenzylcarbamate] out of 15 enantiomeric pairs studied, separated with $R_s \geq 2$. The results showed that the nature of the analyzed compounds plays an important role in chiral discrimination, especially in relation to CSPs based on macrocyclic glycopeptides: 4-aryl-pyrrolidin-2-ones could be resolved with $R_s \geq 2$ on teicoplanin or teicoplanin aglycone chiral selectors, teicoplanin aglycone phase was able also to separate enantiomers of 4-aryl-substituted acetate derivatives, whereas 4-aryl-substituted acetamide derivatives only could be resolved on vancomycin phase.

Keywords Pyrrolidin-2-one derivatives · Enantioseparation · HPLC · Chiral stationary phase · Normal-phase mode

Introduction

Since the discovery of piracetam its structural analogs based on pyrrolidin-2-one pharmacophore have aroused a great interest, and the structural modification of substituents in the 2-pyrrolidone ring remains an active research field of medicinal chemistry [1, 2]. Introduction of a substituent into the heterocycle creates a chiral center (the compound will exist as two enantiomers), however, pharmacological activity is normally associated with single enantiomer [3]. Thus, it is necessary to search for separation methods for the enantioresolution of chiral derivatives of 4C-substituted pyrrolidin-2-ones.

It is known that for the separation of enantiomers the use of chiral stationary phases (CSPs) has become the most popular tool for determination of the enantiomeric purity of different chiral organic compounds [4]. Due to the complexity and lack of predictability in chiral separations, column screening remains the gold standard to initiate chiral method development for active pharmaceutical ingredients and synthetic intermediates [5]. Phases based on the phenylcarbamates or benzoates of polysaccharides are the most dominant and widely used CSPs [6, 7]. Furthermore, our previous studies have shown that phenylcarbamates of amylose as chiral selectors, together with mobile phases consisting of ethanol and *n*-hexane mixtures, are the most effective for separation of racemic 4C-substituted pyrrolidine-2-one derivatives [8, 9]. The best result ($R_s \geq 2$ for 80% or 12 of 15 enantiomeric pairs) was observed on immobilized amylose *tris* (3-chloro-4-methylphenylcarbamate) and coated amylose *tris* (5-chloro-2-methylphenylcarbamate) CSPs [9].

To extend this research, comparative HPLC study on different type chiral stationary phases was performed. First of all, two commercially available immobilized polysaccharide-based *Chiralpak IC* (**IC**) and *Chiralpak IH* (**IH**) columns were tested. The high enantiorecognition ability of cellulose

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tris (3,5-dichlorophenylcarbamate) chiral selector (CS) is well known [10, 11]. Therefore, an immobilized **IC** column was chosen for our study, even though our previous studies showed weaker chiral discrimination on the coated cellulose-based phases [11]. The **IH** phase is one of the latest additions to the family of immobilized CSPs and represents a significant improvement over the coated *Chiralpak AS* stationary phase, offering wider solvent versatility and robustness [12]. **IH** was chosen due to its amylose backbone (found superior in our previous studies), combined with a different type of ligand—(S)-α-methylbenzylcarbamate (in contrary to phenylcarbamates), giving hope, that this CS could provide specific chiral recognition for racemic 4C-substituted pyrrolidine-2-one derivatives.

In addition to polysaccharides, another group of successful chiral selectors in use today are known to be macrocyclic glycopeptides, commercially available under the tradename *Chirobiotic*. One of the unique characteristics of macrocyclic glycopeptide CSPs is the complementary effect among these CSPs [13]. Macrocyclic glycopeptide CSPs are multi-modal, meaning a variety of mobile phase types can be used to initiate selectivity. Moreover, these phases can be switched from one mobile phase system to another without any deleterious effect. Typically, the highest success rate in enantioseparations of pharmaceutical compounds is achieved under both reversed-phase and polar ionic mode. However, elution under polar organic and normal-phase conditions also occurs on macrocyclic glycopeptide CSPs [14]. Normal-phase elution on macrocyclic glycopeptide CSPs is used mainly for neutral compounds [13]. For example, the best separation of chiral dihydrofurocoumarins was achieved under normal-phase mode on *Chirobiotic T*, *TAG* and *R* [15]. Considering that chiral 4C-substituted pyrrolidine-2-one derivatives **1**–**3** are neutral, separations were performed on four macrocyclic glycopeptide CSPs (**V2** with vancomycin, **R** with ristocetin A, **T** with teicoplanin, and **TAG** with teicoplanin aglycone) in isocratic normal-phase mode. Effect of the type of chiral stationary phase (polysaccharide *vs.* macrocyclic glycopeptide with the same type of mobile phase ethanol/*n*-hexane) as well as the effect of the nature of analytes **1**–**3** on enantiomer retention, resolution and elution order was studied in this investigation.

Materials and Methods

Reagents and Standards

Hexane for HPLC (≥97.0%), and 1,3,5-tri-*tert*-butylbenzene were purchased from Sigma–Aldrich (Steinheim, Germany). Anhydrous ethanol (99.8%) was obtained from Fisher Scientific (Loughborough, UK). Racemic compounds and enantiomers were synthesized at the Latvian Institute of Organic Synthesis (Riga, Latvia).

Chromatographic System and Conditions

Experiments were performed on Waters Alliance (Waters Corporation, Torrance, CA, USA) LC system equipped with 2695 separation module with quaternary pump, degasser, autosampler, and column heater. Waters 2489 dual λ absorbance detector was used for the analysis. The output signal in LC system was monitored and processed using Waters Empower 2 software.

Separation was performed on immobilized polysaccharide-based columns {*Chiralpak IC* (here and further abbreviation **IC**) packed with cellulose *tris* (3,5-dichlorophenylcarbamate) and *Chiralpak IH* (**IH**) based on amylose *tris* [(S)-α-methylbenzylcarbamate]; purchased from Chiral Technologies Europe (Illkirch, France)}, and macrocyclic glycopeptide columns {*Chirobiotic V2* (**V2**) with vancomycin as CS, *Chirobiotic R* (**R**) with ristocetin A, *Chirobiotic T* (**T**) with teicoplanin, and *Chirobiotic TAG* (**TAG**) with teicoplanin aglycone CS; purchased from Supelco (Darmstadt, Germany)}. All columns within this study are 250 × 4.6 mm I.D., particle size 5 µm.

Ethanol (EtOH) mixtures with hexane (HEX) were used as mobile phases. The proportion of each mobile phase component was always measured by volume. Equilibration time is defined as 60 min. In order to confirm results, a minimum of three replicate injections were carried. 1,3,5-Tri-*tert*-butylbenzene was used as column void time marker.

The chromatographic runs were performed at flow rate 1.0 mL/min, and a column temperature of 25 °C. Detection was accomplished via measurement of the UV absorption at 210 nm. The injection volume was 10 µL. All analytes have been dissolved in the mobile phase before injection and analytical sample concentration was 1 mg mL^{-1}. The enantiomeric elution order on the CSPs was established by analyzing racemic mixture and individual *R*-enantiomer samples.

Results and Discussion

Enantioseparation of 4C-substituted pyrrolidin-2-one derivatives (**1**–**3;** Fig. 1), differing with both the substituent at position 4C (**a–e**), and the substituent at N (**1–3**) in pyrrolidine-2-one cycle, were tested in chromatographic systems consisting of ethanol/*n*-hexane mobile phases and commercially available immobilized CSPs, such as polysaccharide-based **IC** (*tris* (3,5-dichlorophenylcarbamate) as CS) and **IH** (amylose *tris* [(S)-α-methylbenzylcarbamate] as CS), macrocyclic glycopeptide-based **V2** (vancomycin as CS), **R** (ristocetin A as

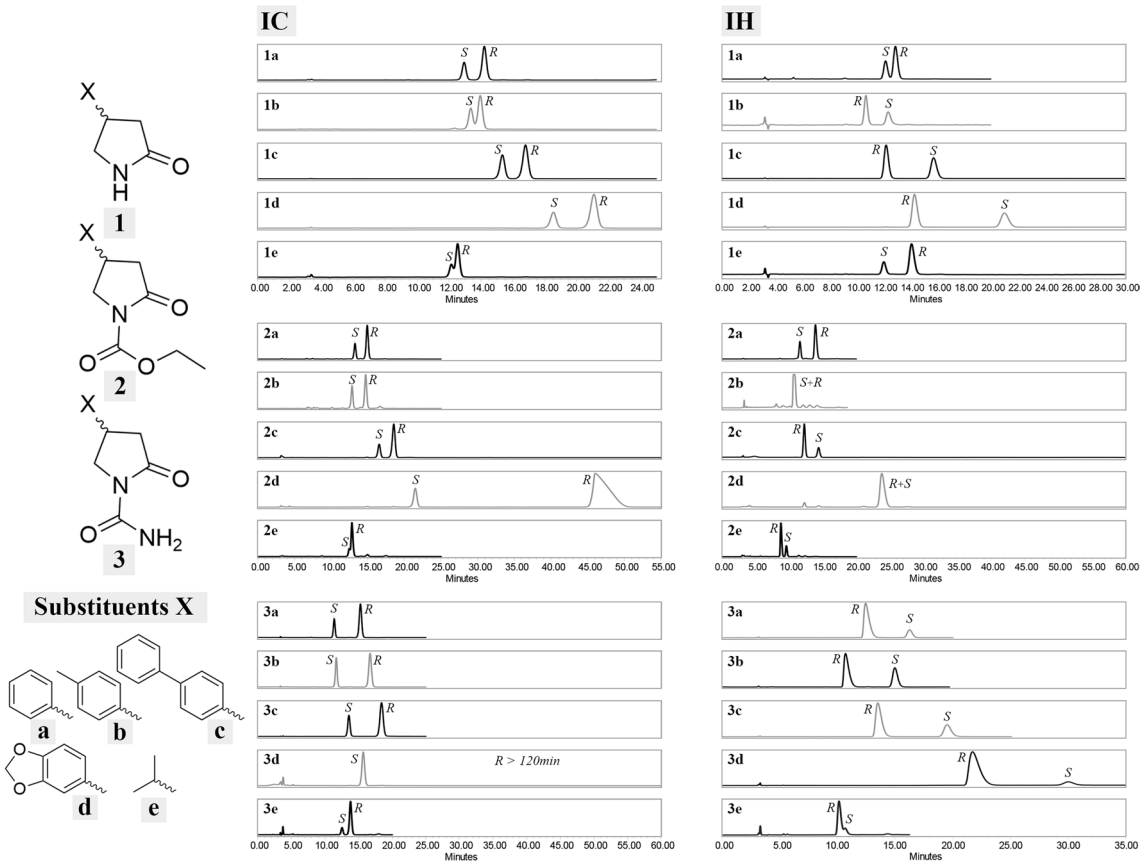

Fig. 1 Chemical structure of 4C-substituted pyrrolidin-2-ones **1a–e**, ethyl 2-(2-oxopyrrolidin-1-yl) acetates **2a–e** and 2-(2-oxopyrrolidin-1-yl) acetamides **3a–e**; and these analyte chromatographic behavior on polysaccharide-based CSPs **IC** and **IH** with mobile phase ethanol/*n*-hexane

CS), **T** (teicoplanin as CS), and **TAG** (teicoplanin aglycone as CS). Fixed retention factor value ($k \sim 3$ for the first eluted enantiomer of compounds **1a**, **2a** and **3a**) was set by adjusting the concentration of EtOH in *n*-hexane for each experiment (Table 1). The experimental results are presented in Tables S1–S6 (Electronic Supplementary materials).

Polysaccharide-Based Chiral Stationary Phases

Chromatographic behavior of analytes **1–3** (Fig. 1) was studied on columns **IC** (Table S1) and **IH** (Table S2) with eluents, consisting of mixture of ethanol/*n*-hexane (Table 1).

4C-Substituted Pyrrolidin-2-Ones

Only three out of five enantiomeric pairs of pyrrolidine-2-ones **1** could be separated with $R_s \geq 2$ on cellulose-based **IC** (mobile phase 25% EtOH/75% Hex; Table 1). Poor resolution was observed for 4-isopropyl-substituted **1e** ($R_s < 0.5$), and for 4-(*p*-tolyl)-substituted **1b** ($R_s = 1.1$). The latter is apparently associated with a stronger retention of the *S*-enantiomer **1b**, as compared to the *S*-enantiomer of 4-phenyl-substituted **1a** (Fig. 1). In all cases, *S*-enantiomers are eluted first on **IC** columns.

On methylbenzylcarbamate containing **IH** CSP, mixture of 70% EtOH in *n*-hexane was necessary to retain compound **1a** with $k \sim 3$ (Table 1). This strong retention may have occurred due to strong π–π interactions between aromatic ring in the CSP and aromatic ring system in analytes **1a**–**d** structure. However, comparing the poor enantioseparation of 4-phenyl-substituted **1a** ($R_s = 1.3$) with the resolution of 4-isopropyl-substituted **1e** (similar retention, $R_s = 3.4$), suggests, that enantioseparation of compounds **1** is more likely driven by intermolecular hydrogen bonds in combination with steric effects, rather than π–π- interactions alone. According to Fig. 1, among 4C-substituted pyrrolidine-2-ones **1**, compound **1e** shows the weakest retention on phenylcarbamate **IC** phase, whereas on (*S*)-methylbenzyl-carbamate-based **IH**, *R*-enantiomer of **1e** ($k \sim 3.60$) retains stronger than 4-phenyl-substituted **1a** ($k \sim 3.21$), and retention of *S*-enantiomers of **1e** ($k \sim 2.93$) and **1a** ($k \sim 2.97$) differs only slightly.

Our previous experiments showed that compounds containing bulkier alkyl substituent in pyrrolidin-2-one cycle

Table 1 First eluted enantiomer and enantioresolution with mobile phase ethanol/*n*-hexane

Compound	CSP											
	IC		**IH**		**V2**		**R**		**T**		**TAG**	
	EtOH, v/v%	First eluted enantiomer and resolution	EtOH, v/v%	First eluted enantiomer and resolution	EtOH, v/v%	First eluted enantiomer and resolution	EtOH, v/v%	First eluted enantiomer and resolution	EtOH, v/v%	First eluted enantiomer and resolution	EtOH, v/v%	First eluted enantiomer and resolution
1a[a]	25	***S****	70	*S*	20	*nr*	40	***R****	55	***R****	70	***R****
1b		*S*		***R****		*nr*		***R****		***R****		***R****
1c		***S****		***R****		*nr*		*R*		***R****		***R****
1d		***S****		***R****		*nr*		*R*		***R****		***R****
1e		*S*		***S****		*nr*		*nr*		*R*		*nr*
2a[a]	20	***S****	40	***S****	10	*nr*	15	*nr*	15	***R****	20	***R****
2b		***S****		*nr*		*R*		*nr*		*R*		***R****
2c		***S****		***S****		*R*		*nr*		***R****		***R****
2d		***S****		*nr*		*R*		*nr*		*R*		***R****
2e		*S*		***S****		*nr*		*ns*		*nr*		*nr*
3a[a]	45	***S****	35	***R****	55	***S****	65	*S*	60	*nr*	70	*R*
3b		***S****		***R****		***S****		*S*		*nr*		*R*
3c		***S****		***R****		***S****		*S*		*nr*		*R*
3d		***S****		***R****		***S****		*S*		***S***		*nr*
3e		***S****		*R*		*S*		*S*		*nr*		*nr*

nr no resolution

*$R_s \geq 2$

[a]Retention factor, *k*, value of the first eluted enantiomer ~ 3

(4-isopropyl-substituted **1e** resolved with R_s = 0.9 vs. 4-isobutylpyrrolidin-2-one with R_s = 2.9) improved enantioresolution [8]. Chromatographic behavior of the above mentioned compounds on **IC** and **IH** CSPs was studied, and poor enantioseparation of 4-isobutylpyrrolidin-2-one (R_s < 0.5) was observed on **IH** phase, while no resolution was achieved on **IC** phase (Fig. S1). It is possible that the bulky nature of the CS in **IH** and **IC** phases creates such steric environment that reduced the chiral recognition of 4-isobutylpyrrolidin-2-one.

Enantiomers of four out of five pyrrolidine-2-ones **1** could be separated (with $R_s \geq 2$) on **IH** column (Table 1). Despite the fact that none of the previously studied CSPs [8, 9] were capable to baseline separate 4-isopropyl-substituted pyrrolidin-2-one **1e**, the **IH** phase was able to separate enantiomers with $R_s > 2$.

By providing alternate selectivity for enantioresolution of various new 4C-substituted pyrrolidin-2-ones **1**, due to its unique chiral recognition, **IH** CSP is a great addition for screening in HPLC method development.

4C-Substituted Ethyl 2-(2-Oxopyrrolidin-1-yl) Acetates

As shown in Fig. 1, good enantioseparation of 4-aryl-substituted acetates **2a—2d** could be achieved on **IC** CSP. Poor resolution (R_s < 0.5) was observed only for enantiomers of 4-isopropyl-substituted **2e** (Table S1). In all cases, *S*-enantiomers of the studied ethyl 2-(2-oxopyrrolidin-1-yl) acetates are eluted first on **IC** column.

Even though immobilized amylose-based **IH** phase was able to resolve 4-isopropyl-substituted **2e** (R_s = 2.11; Table S2), the enantioresolution of compounds **2b** and **2d** was not achieved, possibly, due to the specific steric environment in the **IH** CS.

For this investigation, racemic 4-isobutyl-substituted acetate **2** was synthesized and its chromatographic behavior was compared with 4-isopropyl-substituted acetate **2e** on **IC** and **IH** CSPs (Fig. S2). Increase in resolution of the analyte containing bulkier alkyl substituent in pyrrolidin-2-one cycle (*vs.* acetate **2e**) was observed on both CSPs (**IC,** R_s = 3.01 *vs.* R_s = 0.91; **IH,** R_s = 2.95 *vs.* R_s = 2.11).

The chromatographic behavior of the various 4C-substituted acetate derivatives **2** is difficult to predict for polysaccharide-based CSPs. However, enantiomers of 4 out of 5 studied chiral analytes **2** could be separated on **IC** phase with $R_s \geq 2$ (Table S1).

4C-Substituted 2-(2-Oxopyrrolidin-1-yl) Acetamides

Our previous study has shown that immobilized amylose-based phases with only electron-donating (CH_3) or electron-withdrawing (Cl) substituents at positions 3 and 5 of phenylcarbamate significantly impair the resolution of chiral 2-(2-oxopyrrolidin-1-yl) acetamides **3** [9]. Thus, the separation ability of the immobilized **IC** phase (cellulose derivatized with 3,5-dichlorophenylcarbamate) of enantiomers **3a—3e** was unclear. It was established that 45% EtOH/55% Hex mobile phase was necessary to retain **3a** with k ~ 3 on **IC** phase (Table S1). Enantioresolution with $R_s \geq 2$ was achieved for all acetamide derivatives **3** tested (Table 1). Very strong retention was observed for *R*-enantiomer **3d** (Fig. 1; see also Fig. S3).

When determining enantiomeric purity, it can be considered an advantage, to be able to control the retention order for enantiomers in such way, that the enantiomer with the lowest concentration eluted first. It is known that the *R*-enantiomer of compound **3a** was found to be a more pharmacologically active psycho-stimulating compound than the *S*-enantiomer. Moreover, the cognitive enhancing effect was only observed for *R*-enantiomer [3]. Therefore, **IC** CSP (due to the quicker elution of *S*-enantiomers in all experiments, Table 1) should be the primary candidate in determining the *S*-enantiomers as impurities.

On amylose-based **IH** phase (35% EtOH / 65% HEX; Table 1) 4-aryl-substituted **3a–d** were resolved with R_s ~ 5 (Table S2). More problematic was the separation of 4-isopropyl-substituted **3e** enantiomers (R_s < 0.5). In all cases *R*-enantiomer is eluted first on **IH** phase (Fig. 1).

In general, **IC** and **IH** columns can be considered suitable for enantioseparation of various 4C-substituted 2-(2-Oxopyrrolidin-1-yl) acetamides (see also Fig. S4).

Macrocyclic Glycopeptide-Based Chiral Stationary Phases

The use of macrocyclic glycopeptide phases **V2** (vancomycin as CS; Table S3), **R** (ristocetin A as CS; Table S4), **T** (teicoplanin as CS; Table S5), and **TAG** (teicoplanin aglycone as CS; Table S6) was studied for the resolution of the enantiomers of compounds **1**–**3** (Fig. 2) using ethanol/*n*-hexane containing eluents (Table 1).

4C-Substituted Pyrrolidin-2-Ones

On macrocyclic glycopeptide-based CSP **V2**, pyrrolidin-2-ones **1a—1e** are relatively weakly retained (20% EtOH in *n*-hexane is sufficient to retain **1a** within k ~ 3; Table S3), without enantioresolution (Fig. 2). Stronger retention of 4-aryl-substituted compounds **1a–d** could be achieved by employing other macrocyclic glycopeptide CSPs**: R** (40% EtOH), **T** (55% EtOH) and **TAG** (70% EtOH). On ristocetin CS resolution value for enantiomers of 4-aryl-substituted **1a–d** fluctuates from 1.4 to 2.1 (Table S4), and

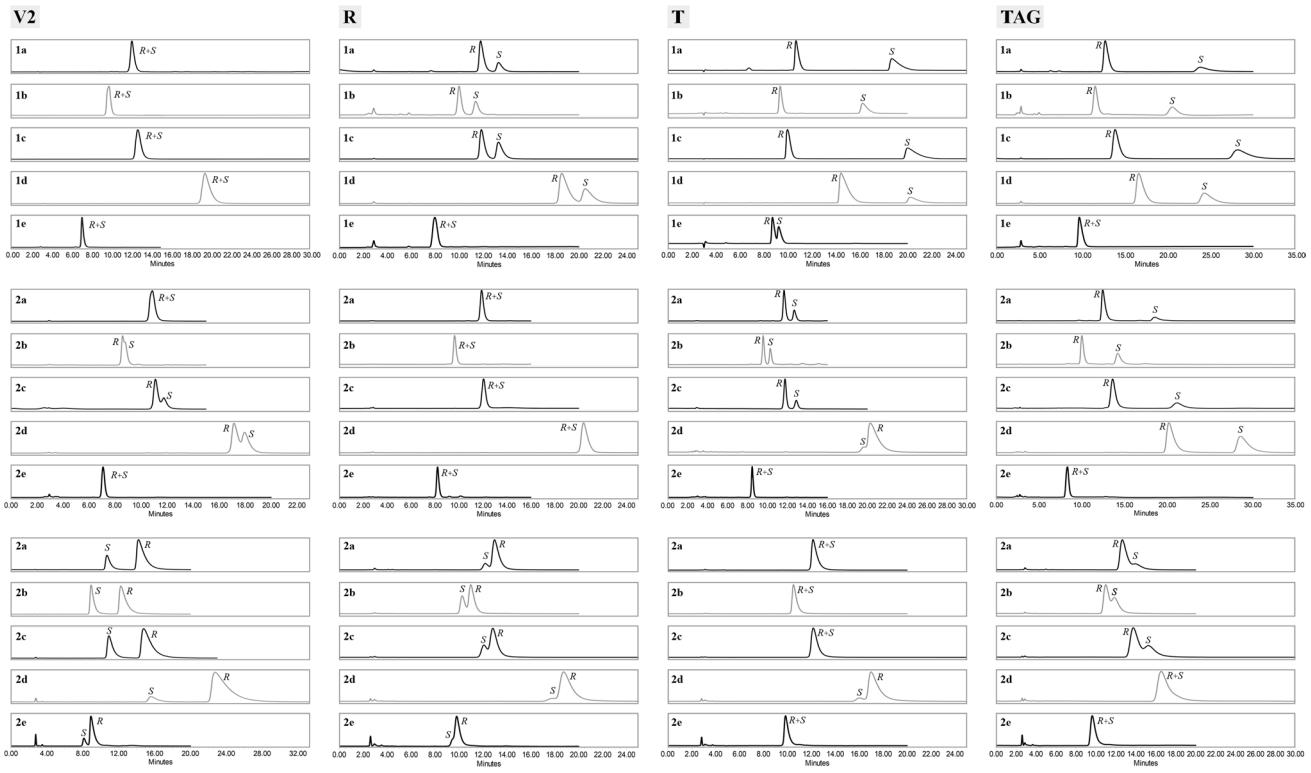

Fig. 2 Chromatograms obtained for racemic 4C-substituted pyrrolidin-2-one derivatives **1–3** on macrocyclic glycopeptide CSPs **V2**, **R, T** and **TAG** with ethanol/*n*-hexane mobile phases

only teicoplanin and teicoplanin aglycone CS**s** were able to resolve **1a–d** enantiomers with $R_s > 3$ (Tables S5, S6). It can be seen (Table 1) that *R*-enantiomers eluted first.

Chromatographic behavior of 4-isopropyl- and 4-isobutylpyrrolidin-2-one on macrocyclic glycopeptide CSPs was compared (Fig. S5). Enantioresolution of compound **1e** was observed only on **T** CSP ($R_s = 1.22$). At the same time, 4-isobutylpyrrolidin-2-one was resolved on **T** CSP with $R_s = 2.90$, and chiral recognition was observed also on **TAG** CSP ($R_s = 1.80$).

In general, macrocyclic glycopeptide-based phases **T** and **TAG** can be used for separation of enantiomers of pyrrolidin-2-ones **1** (Fig. 2).

4C-Substituted Ethyl 2-(2-Oxopyrrolidin-1-yl) Acetates

The chromatographic behavior of 4C-substituted ethyl 2-(2-oxopyrrolidin-1-yl) acetates **2** on macrocyclic glycopeptide CSPs was tested (Tables S3–S6). Mobile phase with 10% EtOH appeared to be sufficient in retaining **2a** with k ~ 3 on **V2** phase, 15% EtOH on **R** and **T**, while 20% EtOH was necessary on **TAG** (Table 1). Poor resolution ($Rs < 0.5$) was observed on vancomycin CS, and no chiral recognition was achieved on ristocetin phase (Fig. 2). Only enantiomers of compounds **2a** and **2c** could be baseline separated ($R_s > 2$; Table S5) on teicoplanin CS, whereas good enantioresolution ($R_s > 4$; Table S6) of chiral compounds **2a–d** was achieved on teicoplanin aglycone phase (*R*-enantiomers eluted first).

None of the macrocyclic glycopeptide-based CSPs studied was able to resolve 4-isopropyl-substituted **2e** (Table 1). Nevertheless, introducing bulkier alkyl substituent (4-isobutyl) slightly improved the enantiorecognition ($R_s = 0.9$) of ethyl 2-(2-oxopyrrolidin-1-yl) acetate **2** on **TAG** CSPs.

In general, **TAG** CSP can be used for separation of enantiomers of 4-substituted ethyl 2-(2-oxopyrrolidin-1-yl) acetates **2** (Table 1).

4C-Substituted 2-(2-Oxopyrrolidin-1-yl) Acetamides

According to Table 1 data mobile phase containing 55% EtOH was sufficient to retain **3a** with k ~ 3 on **V2**, 60% EtOH on **T**, 65% EtOH on **R** and 70% EtOH on **TAG** phases. Despite stronger retention on the last two phases, the best chiral recognition ability of 4C-substituted 2-(2-oxopyrrolidin-1-yl) acetamide derivatives **3** was achieved on vancomycin CSP (*S*-enantiomers eluted first; Fig. 2). Resolution of additional chiral compounds **3** was also tested

on macrocyclic glycopeptide-based CSPs, and **V2** phase showed the best chiral recognition ability (Fig. S7).

In general, **V2** CSP can be used for separation of enantiomers of 4-substituted ethyl 2-(2-oxopyrrolidin-1-yl) acetamide analogs **3** (Table 1).

Conclusions

As shown in this investigation, by employing chiral selector based on cellulose *tris* (3,5-dichlorophenylcarbamate), using ethanol/*n*-hexane containing eluents, 12 out of 15 enantiomeric pairs studied were separated with $R_s \geq 2$. Only two of the previously studied eleven polysaccharide-based phases showed such result. In addition, a specific enantiomer elution order, where the *S*-enantiomer is always eluted first, was observed on the **IC** phase. It was established that, amylose *tris* [(S)-α-methylbenzylcarbamate] chiral selector shows unique chiral recognition, in comparison with the studied phenylcarbamate-based phases. In general terms, both studied polysaccharide-based CSPs seem very promising for the development of HPLC methods for enantioresolution of various new 4C-substituted pyrrolidin-2-one derivatives.

The polysaccharide CSPs are derivatized with moieties that are largely nonpolar, with only the carbamate linkages possessing polar character, while macrocyclic glycopeptides have an abundance of polar groups. However, results showed that the concentration of ethanol in mobile phase mainly depends on nature of the compounds. The type of the analytes played an important role in the chiral discrimination, especially on macrocyclic glycopeptide-bases CSPs. Although, normal-phase elution is typical for polysaccharide-based CSPs, whereas reversed and polar ionic modes are most commonly used on macrocyclic glycopeptide CSPs. Enantioseparation of 4C-substituted pyrrolidin-2-one derivatives under normal-phase elution was achieved on both types of studied CSPs. It was established that 4-aryl-pyrrolidin-2-ones could be resolved with $R_s \geq 2$ on teicoplanin or teicoplanin aglycone chiral selectors**,** teicoplanin aglycone phase was also able to separate enantiomers of 4-aryl-substituted ethyl 2-(2-oxopyrrolidin-1-yl) acetates, whereas 4-aryl-substituted ethyl 2-(2-oxopyrrolidin-1-yl) acetamides could only be resolved on vancomycin phase.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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